DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/20/10 has been entered.

[2] Claims 12, 22, 31, and 71 are pending in the application.

[3] Applicant's amendment to the claims, filed on 8/20/10, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's remarks filed on 8/20/10 in response to the final Office action mailed on 2/22/10 have been fully considered and are deemed to be persuasive to overcome at least one rejection and/or objection previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Rejections and/or objections previously applied to claims 17, 21, 36, 40, and 72 are withdrawn solely in view of the instant amendment to cancel these claims.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objection

[6] Claim 71 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 12. When two claims in an application are duplicates or else are so close in

content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, Second Paragraph

[7] Claims 12, 22, 31, and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "reduced...LKB1 activity...wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene" in claims 12 (claim 22 dependent therefrom), 31, and 71 is a relative term which renders the claim indefinite. The term "reduced...LKB1 activity...wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In the absence of the recitation of a reference level of LKB1 activity and/or a reference LKB1 gene sequence such that one can determine whether or not a particular cell has a reduced LKB1 activity, the claims are broadly and reasonably interpreted as encompassing *any* cancer or cell.

RESPONSE TO ARGUMENT: Beginning at p. 4 of the instant remarks, applicant argues the rejection is obviated by amendment.

Applicant's argument is not found persuasive. The amendment to recite, "wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene" is acknowledged, however, the claims remain indefinite because there is no antecedent basis for the term "the LKB1 gene" and it is unclear as to the intended reference nucleotide sequence of "the LKB1 gene" and corresponding LKB1 activity, such that one of skill in the art could determine whether or not an LKB1 gene of a cell has a mutation and/or a deletion and with reduced LKB1 activity.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description and scope of enablement rejections of claims 12, 22, and 31 under 35 U.S.C. 112, first paragraph, are withdrawn in view of the instant amendment to claims 12 and 31 to limit the "compound that increases AMP activated protein kinase (AMPK) activity in the subject or in cells thereof" to being phenformin. Phenformin is well-known in the prior art and its antineoplastic and/or chemotherapy-potentiating activity is also well-known in the prior art as shown by the references of Dilman et al. (*Arch Geschwulstforsch* 48:1-8, 1978; cited in Form PTO-892 mailed on 4/14/09), Dilman et al. (*Gerontology* 26:241-246, 1980; cited in Form PTO-892 mailed on 4/14/09), Anisimov (*Ann. NY Acad. Sci.* 621:385-400, 1991; cited in Form PTO-892 mailed on 4/14/09), Dilman et al. (*Cancer Letters* 7:357-361, 1979; cited in Form PTO-892 mailed on 4/14/09), Shikhman et al. (*Vopr. Onkol.* 27:67-69, 1981), Cohen et al. (*Oncology* 33:257-259, 1976), Bespalov (*Vopr. Onkol.* 30:55-59, 1984), Bespalov et al. (*Biull. Eksp. Biol. Med.* 100:73-76, 1985), Bespalov et al. (*Vopr. Onkol.* 34:80-83, 1988), and Byczkowski et al. (*Can. Res.* 42:3592-3595, 1982).

[9] Claims 12, 22, 31, and 71 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 12 and 71 are drawn to a method for treating cancer, comprising administering to a genus of subjects having a cancer having reduced or absent LKB1 activity an effective amount of phenformin, wherein the reduction of LKB 1 activity is due to a mutation or deletion of the LKB1 gene.

Claim 22 limits the method of claim 12 to further comprising subjecting the cancer of the genus of subjects or cells thereof to a cell death stimulus.

Claim 31 is drawn to a method for promoting apoptosis of a genus of cells having reduced or absent LKB1 activity, comprising contacting the cells with phenformin, wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene. The recited "cells" are interpreted as being cells within a subject, *e.g.,* a human subject.

Regarding claims 12, 22, and 71, the recited "subject having a cancer having reduced or absent LKB1 activity…wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene" is an essential and critical feature of the claimed invention.

Similarly in claim 31, the recited "cells having reduced or absent LKB1 activity…wherein the reduction of LKB1 activity is due to a mutation or deletion of the LKB1 gene" is an essential and critical feature of the claimed invention.

In this case, the specification discloses only a single subject having a cancer that has reduced or absent LKB1 activity, *i.e.,* a cancer patient with Peutz-Jeghers syndrome. Indeed, at the time of the invention, it was well known in the prior art that patients with Peutz-Jeghers syndrome have an increased incidence of malignancy, including cancers of the breast, gut, pancreas, ovary, and endometrium, with relatively greater risk for breast and gynecologic cancer as shown by Forster et al. (*J. Clin. Pathol.* 53:791-793, 2000) at p. 90, columns 1-2. However, as acknowledged by applicant, some cancers may very well have increased LKB1 activity (instant remarks at p. 10) and as such, a skilled artisan would recognize that it is unpredictable as to whether or not a cancer has or does not have reduced or absent LKB1 activity. Other than the correlation between a cancer patient with Peutz-Jeghers syndrome and the characteristic of having a cancer that has reduced or absent LKB1 activity, the specification fails to teach or suggest any other species of subjects having a cancer that has reduced or absent LKB1 activity. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the *entire* genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Here, the disclosed representative species fails to describe all members of the recited genus of subjects and cells. Given the lack of description of a representative number of subjects and cells to reflect the variation among the members of the genus, the specification fails

to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 102/103

[10] The rejection of claims 12, 31, and 71 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dilman et al. (*Arch Geschwulstforsch* 48:1-8, 1978; cited in Form PTO-892 mailed on 4/14/09; hereafter referred to as "Dilman1") OR Dilman et al. (*Gerontology* 26:241-246, 1980; cited in Form PTO-892 mailed on 4/14/09; hereafter referred to as "Dilman2") as evidenced by Shen (*Clin. Cancer Res.* 8:2085-2090, 2002; cited in Form PTO-892 mailed on 4/14/09) and Zhang et al. (*Am. J. Physiol. Circ. Physiol.* 293:H457-H466, 2007; cited in Form PTO-892 mailed on 4/14/09; hereafter referred to as "Zhang") is withdrawn. The rejection is withdrawn solely in favor of the new rejection set forth below and not in view of applicant's claim amendment and/or remarks.

[11] The rejection of claim 22 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dilman1 OR Dilman2 as evidenced by Shen and Zhang and as further evidenced by Caraci et al. (*Life Sci.* 74:643-650, 2003; cited in Form PTO-892 mailed on 4/14/09; hereafter referred to as "Caraci") is withdrawn. The rejection is withdrawn solely in favor of the new rejection set forth below and not in view of applicant's claim amendment and/or remarks.

[12] Claims 12, 22, 31, and 71 are newly rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shikhman et al. (*Vopr Onkol.* 27:67-69, 1981; hereafter "Shikhman"), Dilman et al. (*Cancer Letters* 7:357-361, 1979; cited in Form PTO-892 mailed on 4/14/09; hereafter "Dilman3"), or Cohen et al. (*Oncology* 33:257-259, 1976; hereafter "Cohen") as evidenced by Caraci (*supra*).

The reference of Shikhman teaches that administering phenformin to rats inhibited Ehrlich carcinoma cell growth (p. 69).

The reference of Dilman3 teaches phenformin administered to mice potentiated the antitumor effect of cyclophosphamide on transplantable squamous cell cervical carcinoma, hepatoma-22a, and Lewis lung tumor and potentiated the antitumor effect of hydrazine sulfate on rats with transplantable Walker 256 carcinoma (p. 357, abstract).

The reference of Cohen teaches that phenformin enhances the antitumor effect of BCNU in advanced subcutaneously implanted murine L1210 leukemia (p. 257, abstract).

This anticipates claims 12, 31, and 71 as written because, as noted above, in the absence of the recitation of a reference level of LKB1 activity and/or a reference LKB1 gene sequence, the claims are broadly and reasonably interpreted as encompassing *any* cancer in claims 12 and 71 and any cell in claim 31.

This also anticipates claim 22 in view of evidentiary reference Caraci, which teaches that phenformin induces apoptosis of cancer cells (*e.g.,* p. 649, middle).

RESPONSE TO ARGUMENT: Beginning at p. 6 of the instant remarks, applicant addresses the rejection of claims 12, 22, 31, and 71 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dilman1 OR Dilman2 as evidenced by Shen and Zhang, and further evidenced by Caraci, arguing the reference of Shen fails to provide evidence that breast cancer is a cancer having reduced or absent LKB1 expression; neither Dilman1 nor Dilman2 treats existing cancer; and claim 22 requires a combination therapy, not administration of a single compound.

Applicant's argument is not found persuasive. As noted above, the rejection based on the reference of Dilman1 or Dilman2 is withdrawn in favor of a new rejection. Moreover, the examiner maintains that "subjecting the cancer of the subject or cells thereof to a cell death stimulus" is reasonably interpreted to encompass the single step of administering phenformin. Although applicant takes the position that claim 22 requires a combination therapy, the claim does not recite such a limitation and the specification does not appear to define "subjecting the cancer of the subject or cells thereof to a cell death stimulus" as requiring combination therapy.

Claim Rejections - 35 USC § 103

[13] The rejection of claims 12, 22, 31, and 71 under 35 U.S.C. 103(a) as being unpatentable over the combination of Dilman1, Dilman2, and Dilman3 as evidenced by Shen, Zhang, and Caraci is withdrawn. The rejection is withdrawn solely in favor of the

new rejection set forth below and not in view of applicant's claim amendment and/or remarks.

[14] Claims 12, 22, 31, and 71 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Dilman3 (*supra*) in view of Forster et al. (*J. Clin. Pathol.* 53:791-793, 2000; hereafter "Forster"), and Jones et al. (*Cancer* 36:90-97, 1975; hereafter "Jones") and as evidenced by and Caraci (*supra*).

Dilman3 teaches "Combined chemotherapy ... is finding wide application ... Treatment of cancer patients with phenformin has been suggested ... the present study was concerned with the possible potentiation of the antitumor effect of cyclophosphamide by means of phenformin treatment and investigated the combined effect of hydrazine sulfate and phenformin" (pp. 357-358, Introduction). Dilman3 teaches "Our results show that phenformin treatment potentiates the antitumor effect of ... cyclophosphamide and .... hydrazine sulfate. They also confirm the conclusion ... that it is desirable to explore the possibility of improving the results of chemotherapy of tumor patients by giving them a simultaneous course of phenformin" (p. 360, Discussion). Dilman3 does not teach administering phenformin to potentiate chemotherapy for treatment of cancer in a patient with Peutz-Jeghers syndrome.

Forster discloses patients with Peutz-Jeghers syndrome have an increased incidence of malignancy, including cancers of the breast, gut, pancreas, ovary, and endometrium (p. 90, column 1), with relatively greater risk for breast and gynecologic cancer (p. 90, column 2). Forster acknowledges that allele loss occurs relatively frequently at the LKB1 locus in sporadic breast cancer (p. 791, abstract). Forster does

not teach administering phenformin for treatment of breast cancer in a patient with Peutz-Jeghers syndrome.

Jones provides precedent for combination chemotherapy for breast cancer, teaching that "chemotherapy with combinations of several active drugs has, in general, resulted in improved response rates and longer remissions…because useful combinations have at least additive, and potentially synergistic, 'log-kill' effects against cancer" (p. 90, column 2), specifically teaching cyclophosphamide and adriamycin treatment of advanced breast cancer (p. 90, abstract).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Dilman3, Forster, and Jones to administer chemotherapy in combination with phenformin to a cancer patient with Peutz-Jeghers syndrome, *e.g.*, administering cyclophosphamide or cyclophosphamide/adriamycin along with phenformin to a breast cancer patient with Peutz-Jeghers syndrome. Although the combination of references does not teach or suggest "subjecting the cancer…to a cell death stimulus", evidentiary reference Caraci teaches that phenformin induces apoptosis of cancer cells (*e.g.*, p. 649, middle). One would have been motivated to do this because of the teachings of Dilman3 and Jones. One would have had a reasonable expectation of success to administer chemotherapy in combination with phenformin to a cancer patient with Peutz-Jeghers syndrome because of the results of Dilman3, Forster, and Jones.

RESPONSE TO ARGUMENT: Beginning at p. 8 of the instant remarks, applicant addresses the rejection of claims 12, 22, 31, and 71 under 35 U.S.C. 103(a)

as being unpatentable over the combination of Dilman1, Dilman2, and Dilman3 as evidenced by Shen, Zhang, and Caraci, arguing the effects of administering phenformin are unexpected; the Dilman references fail to teach phenformin has an effect on cancers having reduced or absent LKB1 activity; neither Dilman1 nor Dilman2 treats existing cancer; Dilman3 teaches phenformin potentiation only in certain cell types; and the disclosed cancers may very well have had normal or increased LKB1 activity, rather than reduced or absent LKB1 activity.

Applicant's argument is not found persuasive. Contrary to applicant's position, the benefits of administering phenformin to a subject having a cancer, *e.g.,* reducing tumor growth and potentiating the antitumor effect of anti-cancer therapies, were well-known at the time of the invention as shown by the teachings of the Dilman3 reference and are reasonably expected in view of the prior art of Dilman3. Although the teachings of the Dilman3 reference do not appear to specifically direct one to administer phenformin to a patient with a cancer having reduced or absent LKB1 activity, based on the teachings of the Dilman3 reference that phenformin can potentiate the effects of chemotherapy, one would have been motivated to administer a combination of phenformin and a chemotherapy to a patient having Peutz-Jeghers syndrome, *e.g.,* phenformin and cyclophosphamide to a breast cancer patient having Peutz-Jeghers syndrome. In view of the combination of references, *a priori* knowledge of a nexus between AMPK and LKB1 is not required to expect to achieve a beneficial result by administering a combination of phenformin and chemotherapy to a Peutz-Jeghers syndrome patient having cancer.

Conclusion

[15] Status of the claims:

- Claims 12, 22, 31, and 71 are pending.
- Claims 12, 22, 31, and 71 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656